"isolated and purified." The amendment is supported by the specification, which discloses that "[t]echniques for cloning, expressing and purifying [the desaturase] polypeptides are well known to the skilled person." (Page 12, lines 16-17.) Claim 1 also has been amended to recite that the desaturase "comprises" the polypeptide sequence of a), b), or c). This amendment is supported by the specification, which discloses that the desaturase polypeptide "may have an additional N-terminal and/or an additional C-terminal amino acid sequence." (Page 6, lines 9-10.) Claim 1 has been amended to recite that the amino acid sequence of a) is the sequence shown in "SEQ ID NO:2" in place of "Figure 1." The specification discloses that Figure 1 shows the sequence of SEQ ID NO:2. (Page 3, lines 12-13.) Claim 1 has also been amended to recite that the polypeptide having desaturase activity of b) has at least "50% amino acid sequence identity" in place of "32% amino acid sequence identity" with SEQ ID NO: 2. This amendment is supported by the specification, which discloses that the polypeptides of the invention have "at least 50% amino acid sequence identity." (Page 4, lines 9-10.) Claim 1 has further been amended to recite that the polypeptide having desaturase activity of c) "is at least 150 amino acids long" in place of "at least 100 amino acids long." This amendment is also supported by the specification at page 4, lines 22-23.

New claim 39 is directed to an isolated and purified Δ^6 desaturase polypeptide. This new claim is supported by originally filed claim 7. Claim 39 recites that the Δ^6 desaturase comprises the amino acid sequence as shown in SEQ ID NO:2 with no more than five conservative amino acid substitutions. This recitation is supported by the specification, which discloses that a Δ^6 desaturase polypeptide may have "less than 5 differences [in amino acid sequence]." (Page 4, lines 16-18.) The specification also discloses that these substitutions may be "'conservative' or

'semi-conservative' amino acid substitutions." (Page 8, lines 3-4.)

New claim 40 recites that the Δ^6 desaturase has one conservative amino acid substitution. New claim 40 is supported by the specification which discloses that a polypeptide of the invention may have a "substitution of one or more amino acids with one or more other amino acids." (Page 7, lines 15-16.)

New claim 41 recites that the Δ^6 desaturase comprises the amino acid sequence as shown in SEQ ID NO:2. Claim 41 is supported by originally filed claim 1.

New claim 42 recites that the Δ^6 desaturase polypeptide of SEQ ID NO:2 is linked to a moiety. Claim 42 is supported by originally filed claim 14.

New claim 43 recites that the Δ^6 desaturase polypeptide of SEQ ID NO:2 further comprises a signal sequence. This amendment is supported by the specification at page 6, lines 20-22.

None of these amendments introduce new matter.

The Rejection of Claims 1-14 and 23 Under 35 U.S.C. § 101

Claims 1-14 and 23 have been rejected under 35 U.S.C. § 101 for being directed to non-statutory subject matter. This rejection is respectfully traversed.

The Office Action asserts that the rejected claims are directed to non-statutory subject matter because they recite naturally occurring proteins that read on products of nature. Independent claim 1 has been amended to recite that the claimed polypeptides are "isolated and purified." Thus amended independent claim 1 and dependent claims 2-14 and 23 are directed to statutory subject matter. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1-14 and 23 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-14, and 23 are rejected under 35 U.S.C. § 112, second paragraph as not distinctly claiming the subject matter that applicant regards as his invention. The rejection is respectfully traversed.

The Office Action asserts that the claims are unclear because the recitation "the amino acid sequence shown in Figure 1" does not refer to an amino acid sequence by sequence identification number. Claim 1 has been amended to recite the amino acid sequence shown in "SEQ ID NO: 2." Withdrawal of the rejection to claim 1 and dependent claims 2-14 and 23 is respectfully requested.

The Rejection of Claims 1-14 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 1-14, and 23 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not sufficiently described in the specification. The rejection is respectfully traversed.

Amended claim 1, the independent claim of the rejected claim set, is directed to a polypeptide having desaturase activity. The polypeptide (a) has the amino acid sequence as shown in SEQ ID NO:2, (b) has one or more amino acid deletions, insertions, or substitutions and at least 50% amino acid sequence identity with the polypeptide as defined in (a), or (c) is a fragment of the polypeptide of (a) or (b) which is at least 150 amino acids long. The Office Action asserts that the claimed genus of polypeptides is not adequately described because the genus includes modified desaturase polypeptides that are not described in the specification. (Paper 14, page 4, lines 25-26.)

To satisfy the written description requirement, the specification must describe the

claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d. 1555, 1563-1564 (Fed. Cir. 1991). The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (January 5, 2001); approved in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). The specification meets this standard.

Claims 1, 8-12, 14, and 23 are each directed to a polypeptide that has desaturase activity. The recited genus of desaturase polypeptides is described in the specification by relevant characteristics, such as by structure or chemical properties. Some polypeptides of the genus have the amino acid sequence as shown in SEQ ID NO:2 (claim 1(a), line 3). SEQ ID NO:2 is disclosed in the specification. Thus the full structure of (a) is described in the specification. Other polypeptides of the genus comprise one or more amino acid deletions, insertions, or substitutions and are at least 50% identical to SEQ ID NO:2 (claim 1(b), lines 4-5). Other polypeptides of the genus comprise a fragment of (a) or (b) that is at least 150 amino acids in length (claim 1(c), lines 6-7). The specification also describes the structure of desaturase polypeptides (b) and (c) via their relationship to SEQ ID NO:2. Thus the specification describes sufficient identifying characteristics of the claimed species of polypeptides with desaturase activity that one skilled in the art would conclude that the inventors had possession of the polypeptides of claims 1, 8-12, 14, and 23.

Claims 2-7 recite additional identifying characteristics of the claimed polypeptides. These characteristics are described in the specification with sufficient detail that one of skill in the art would understand that applicants had possession of the polypeptides of claims 2-7.

Claim 2 recites that the polypeptide having desaturase activity has a cytochrome domain. The specification teaches that a cytochrome domain "can be defined as an electron-transporting domain that contains a heme prosthetic group." (Page 5, lines 11-12.) Thus the specification describes the polypeptides of claim 2 as including functional (electron transport activity) and chemical (a heme group) properties. Claim 3 further recites that the polypeptide has a cytochrome b_5 domain. The specification discloses that such a domain "includes a H-P-G-G-X_{15}-F-X_{3-6}-H (SEQ ID NO:3), where X is any amino acid, motif." (Page 5, lines 13-14.) Thus the cytochrome domain of the polypeptide of claim 3 is further described in the specification by a specific amino acid sequence.

Claim 4 recites that the polypeptide has at least one histidine box. Claim 5 recites that the polypeptide has at least three histidine boxes. The specification describes a histidine box as containing an amino acid sequence Q-X-X-H-H. (Page 18, line 23.) The specification also discloses that a histidine box "may have an H-Q substitution." (Page 5, line 21.) Thus the specification discloses additional, distinguishing structural characteristics of the polypeptide of claims 4 and 5.

The specification further describes the polypeptides of claims 6 and 7 by functional properties. Claim 6 recites that the polypeptide having desaturase activity is a front-end desaturase. The specification discloses that "'front-end' desaturation can [be] defined as the final desaturation on the fatty acid chain, usually introducing double bonds between a pre-

existing bond and the Δ-end of the carboxy group." (Page 23, line 28 to page 24, line 2.) Claim 7 recites that the polypeptide with desaturase activity is a Δ^6 desaturase. These polypeptides desaturate at the Δ^6 position of fatty acids. (Page 2, lines 2-5.) Each of dependent claims 2-7 recites additional relevant identifying characteristics of the polypeptides.

Originally filed claim 13 and new claims 39-43 recite structural features that are explicitly described in the specification. Claim 13 recites that the polypeptide consists of the amino acid sequence of SEQ ID NO:2 or a part thereof. The specification discloses SEQ ID NO:2 and thus its full structure. New independent claim 39 is directed to an isolated and purified Δ^6 desaturase polypeptide comprising the amino acid sequence of SEQ ID NO:2 with no more than five conservative amino acid substitutions. A conservative amino acid substitution is described in the specification as the replacement of one amino acid with another that has similar chemical properties. See page 7, line 21 to page 8, line 2. The description of the amino acid sequence of SEQ ID NO:2 and the description of conservative amino acid substitutions would have conveyed to one of skill in the art that applicants had possession of the subject matter to which originally filed claim 13 and new claims 39-43 are directed at the time the application was filed.

Withdrawal of this rejection to claims 1-14 and 23 is respectfully requested.

The Rejection of Claims 1-14 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 1-14, and 23 are rejected under 35 U.S.C. § 112, first paragraph as not being enabled for their full scope. The rejection is respectfully traversed.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue

experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The test is not merely quantitative, because a considerable amount of experimentation is permissible if the experimentation is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The present specification and the level of skill in the art provide the skilled practitioner with sufficient guidance to practice the claimed invention without having to resort to undue experimentation.

The Office Action asserts that the claims are not enabled because they have a broad scope and:

> [I]t is not a routine in the art to clone all possible desaturases from all natural or man made sources and select those that are at least 32% identical to SEQ ID NO:2. Also, it is not a routine experimentation in the art to modify SEQ ID NO:2 by making deletions, insertions and substitutions resulting in a protein that has 32% identity to SEQ ID NO:2 and desaturase activity. It is not possible to select all [of the] at least 100 amino acid fragments of such desaturases that retain the desaturase activity and any parts of such desaturases that retain desaturase activity. [The] [p]robability of success in making the invention is very low.

Paper 14, page 6, lines 11-18. In the same paragraph, however, the Patent Office acknowledges that the methods of gene cloning and manipulation are well developed and that the level of skill in this art is high. (Paper 14, page 6, lines 10-11,) Given the knowledge in the art and the level of skill in the art, any experimentation needed to prepare the claimed desaturase polypeptides would merely involve the practice of routine methods. The practice of routine methods is not undue experimentation.

The Office Action further asserts that the specification does not adequately guide one of skill in the art to make and use the broadly claimed desaturase polypeptides. First, the Office Action alleges that the specification does not disclose which desaturase protein a person of skill in the art should choose. (Paper 14, page 6, lines 22-24.) Claim 1 recites a polypeptide with desaturase activity that has an amino acid sequence as shown in SEQ ID NO:2 and polypeptides that contain specific, recited variations from SEQ ID NO:2. Thus the specification and claims provide a starting point (SEQ ID NO:2) from which to choose a desaturase polypeptide.

Second, the Office Action alleges that the specification lacks adequate guidance to make and use the claimed invention because it does not disclose the rules for performing substitutions, deletions, or insertions in the desaturase amino acid sequence that will still produce a protein with desaturase function. (Paper 14, page 6, lines 24-26.) The specification offers the following guidance for performing amino acid substitutions: "The skilled person is aware that various amino acids have similar characteristics. One or more such amino acids of a polypeptide can often be substituted by one or more other such amino acids without eliminating a desired property of that polypeptide (such as desaturase activity)." (Page 7, lines 17-20.) The specification further provides guidance as to which specific amino acid substitutions can be performed to arrive at functional desaturases. (Specification at page 7, line 21 through page 8, line 2.) As noted above, the Office has acknowledged that the level of skill in the art at the time the application was filed was high and that the methods of cloning and manipulating gene sequences were well known. Thus functional polypeptides that contain amino acid substitutions relative to SEQ ID NO:2 could be produced by routine experimentation.

Functional desaturase polypeptides containing deletions relative to SEQ ID NO:2 also

could be produced without undue experimentation. The level of skill in the art prior to the November 24, 1997 effective filing date of the application was such that it would have been routine for one of ordinary skill to make deletions in the amino acid sequence as shown in SEQ ID NO:2 and to determine whether the resultant protein retained desaturase activity. (See Appendices 1-5.) Bresciani *et al.* (*Biochem. J.* (1997) *327*, 811-818; Appendix 1) truncated the mannose-6-phosphate receptor to determine which amino acid residues are required for its localization on the cell surface. Ray *et al.* (*J. Biol. Chem.* (1997) *272*, 31355-31361; Appendix 2) tested a series of carboxyl-terminal truncated human calcium receptors for their ability to be expressed on the cell-surface and transduce intracellular signaling in response to calcium. Drachman *et al.* (*Proc. Natl. Acad. Sci. USA* (1997) *94*, 2350-2355; Appendix 3) produced eight different carboxyl-terminal deleted thrombopoietin receptors and determined which proteins remained functional or caused tyrosine phosphorylation. Zahn *et al.* (*Proc. Natl. Acad. Sci. USA* (1996) 93, 15024-15029; Appendix 4) expressed fragments of the chaperone protein GroEL and tested its ability to bind to and refold proteins. Ruaro *et al.* (*Proc. Natl. Acad. Sci. USA* (1997) *94*, 4675-4680; Appendix 5) produced deletion mutants of p53 and tested their ability to bind to specific sequences of DNA and cause growth arrest in cells. One of skill in the art could similarly make deletions in the desaturase polypeptide and test its activity. The specification discloses tests to determine desaturase activity. See page 5, lines 25-28; page 22, lines 1-17; and page 23, lines 2-6. Thus, the experimentation required to produce and test the deleted desaturase polypeptides would merely be routine to those of skill in the art and is not undue.

Functional desaturase polypeptides containing insertions relative to SEQ ID NO:2 also could be produced without undue experimentation. The specification provides guidance for

performing insertions in the desaturase amino acid sequence that will still produce a protein with desaturase function. The specification discloses that "[a]mino acid insertions . . . may be done to alter the nature of the polypeptide (e.g. to assist in identification, purification or expression)." (Page 8, lines 10-12.) These insertions may alter the polypeptide to "provide some protection against proteolytic cleavage." (Page 6, lines 17-18.) Other insertions can be, for example, "a signal sequence . . . to direct the transport of the polypeptide to a particular location within a cell or to export the polypeptide to a particular location within a cell or to export the polypeptide from the cell." (Page 6, lines 20-22.) The specification also teaches that insertions can be "moiet[ies] capable of being isolated by affinity chromatography." (Page 6, line 23.) Amino acids and amino acid sequences that perform these functions were well-known in the art prior to the effective filing date of the application. Thus, the experimentation required to produce the desaturase polypeptides with amino acid insertions would also merely be routine to those of skill in the art and not undue.

Withdrawal of this rejection to claims 1 and dependent claims 2-14 and 23 is respectfully requested.

The Rejection of Claims 1-14 and 23 Under 35 U.S.C. § 102 (e)

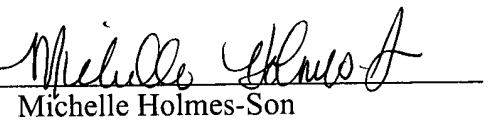
Claims 1-14, and 23 are rejected under 35 U.S.C. § 102 (e) as anticipated by Knutzon *et al.* (U.S. Patent 5,098,809). This rejection is respectfully traversed.

In a telephone conference with Lisa Hemmendinger on November 5, 2002, Examiner Walicka indicated that the rejection had been made in error and would be withdrawn.

Withdrawal of this rejection to claims 1-14 and 23 is respectfully requested.

Respectfully submitted,

Date: January 13, 2003

By: 
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Appendix I. Marked Up Version of the Claims to Sh w the Changes Made

1. (Amended) [A] An isolated and purified polypeptide having desaturase activity, which comprises:

a) [has] the amino acid sequence shown in [Figure 1] SEQ ID NO:2;

b) [has] one or more amino acid deletions, insertions or substitutions relative to a polypeptide as defined in a) above, but has at least [32%] 50% amino acid sequence identity therewith; or

c) [is] a fragment of a polypeptide as defined in a) or b) above, which is at least [100] 150 amino acids long.

13. (Amended) A polypeptide according to claim 1, which consists of the amino acid sequence shown in [Figure 1] SEQ ID NO:2 or a part thereof.

Appendix II. Clean Version of the Pending Claims

1. An isolated and purified polypeptide having desaturase activity, which comprises:

a) the amino acid sequence shown in SEQ ID NO:2;

b) one or more amino acid deletions, insertions or substitutions relative to a polypeptide as defined in a) above, but has at least 50% amino acid sequence identity therewith; or

c) a fragment of a polypeptide as defined in a) or b) above, which is at least 150 amino acids long.

2. A polypeptide according to claim 1, which has a cytochrome domain.

3. A polypeptide according to claim 2, which has a cytochrome b_5 domain.

4. A polypeptide according to claim 1, which has at least one histidine box.

5. A polypeptide according to claim 1, which has three histidine boxes.

6. A polypeptide according to claim 1, which is a front end desaturase.

7. A polypeptide according to claim 1, which is a Δ^6 desaturase.

8. A polypeptide according to claim 1, which occurs naturally in an organism that does not accumulate GLA.

9. A polypeptide according to claim 1, which occurs naturally in a eukaryote.

10. A polypeptide according to claim 1, which occurs naturally in an animal.

11. A polypeptide according to claim 1, which occurs naturally in a nematode.

12. A polypeptide according to claim 1, which occurs naturally in *C. elegans*.

13. A polypeptide according to claim 1, which consists of the amino acid sequence shown in SEQ ID NO:2 or a part thereof.

14. A polypeptide according to claim 1, when covalently linked to another moiety.

23. A polypeptide according to claim 1, for use in medicine.

39. An isolated and purified Δ^6 desaturase polypeptide comprising the amino acid sequence as shown in SEQ ID NO:2 with no more than five conservative amino acid substitutions, wherein the polypeptide has desaturase activity.

40. The polypeptide of claim 39 which has one conservative amino acid substitution.

41. The polypeptide of claim 39 which comprises the amino acid sequence as shown in SEQ ID NO:2.

42. The polypeptide of claim 41 which is covalently linked to a moiety.

43. The polypeptide of claim 41 further comprising a signal sequence.